

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**

(Use as many sheets as necessary)

Complete if Known

| | |
|--------------------------------|----------------|
| Application Number | 10/501,628 |
| Filing Date (I.A. Filing Date) | 01/15/2003 |
| First Named Inventor | Alberto Martin |
| Art Unit | to be assigned |
| Examiner Name | to be assigned |
| Attorney Docket Number | 96700/905 |

Sheet 1 of 4

NON PATENT LITERATURE DOCUMENTS

| Examiner Initials* | Cite No. ¹ | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T ² |
|--------------------|-----------------------|---|----------------|
| | 1 | ARAKAWA H. et al., "Requirement of the Activation-Induced Deaminase (AID) Gene for Immunoglobulin Gene Conversion"; Science, 2002, Vol. 295, pp. 1301-6. | |
| | 2 | BACHL J. et al., "Increased transcription levels induce higher mutation rates in a hypermutating cell line"; J. Immunol, 2001, Vol.166, No. 8, pp. 5051-7. | |
| | 3 | BEMARK M. et al., "The c-MYC allele that is translocated into the IgH locus undergoes constitutive hypermutation in a Burkitt's Lymphoma line"; Oncogene, 2000, Vol. 19, No. 30, pp. 3404-10. | |
| | 4 | DAVIDSON N.O. et al., "Apolipoprotein B: mRNA Editing, Lipoprotein Assembly, and Presecretory Degradation"; Annu. Rev. Nutr., 2000, Vol. 20, pp. 169-93. | |
| | 5 | GREEN N.S. et al., "Immunoglobulin hypermutation in cultured cells"; Immunol. Rev., 1998, Vol.162, pp. 77-87. | |
| | 6 | HARRIS R.S., et al., "AID Is Essential for Immunoglobulin V Gene Conversion in a Cultured B Cell Line"; Curr. Biol., 2002, Vol. 12, pp. 435-8. | |
| | 7 | KINOSHITA K. et al., "Linking class-switch recombination with somatic hypermutation"; Nat. Rev. Mol. Cell Biol., 2001, Vol. 2, pp. 493-503. | |
| | 8 | KOBRIN B.J. et al., "The Somatic Instability of Immunoglobulin Genes in Cultured Cells"; PP. 11-28 (Chapter 2) in Somatic hypermutation in V regions (ed. Steele, E. J.), CRC Press, Boca Raton, Florida, 1990. | |
| | 9 | KUPPERS R. et al., "Mechanisms of chromosomal translocations in B cell lymphomas"; Oncogene, 2001, Vol. 20, No. 40, pp. 5580-94. | |
| | 10 | LIN M.M. et al., "Sequence dependent hypermutation of the immunoglobulin heavy chain in cultured B cells"; Proc. Natl. Acad. Sci. USA, 1997, Vol. 94, No. 10, pp. 5284-9. | |

| | |
|--------------------|-----------------|
| Examiner Signature | Date Considered |
|--------------------|-----------------|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

| | | | | | | |
|--|---|----|---|--------------------------------|----------------|-----------|
| Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i> | | | | Complete if Known | | |
| | | | | Application Number | 10/501,628 | |
| | | | | Filing Date (I.A. Filing Date) | 01/15/2003 | |
| | | | | First Named Inventor | Alberto Martin | |
| | | | | Art Unit | to be assigned | |
| | | | | Examiner Name | to be assigned | |
| Sheet | 2 | of | 4 | Attorney Docket Number | | 96700/905 |

| NON PATENT LITERATURE DOCUMENTS | | | |
|---------------------------------|-----------------------|---|----------------|
| Examiner Initials* | Cite No. ¹ | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T ² |
| | 11 | LIN M.M. et al., "The effects of E-mu, 3'-alpha (hs 1,2) and 3'-kappa enhancers on mutation of an Ig-VDJ-C-gamma-2a Ig immunoglobulin heavy gene in cultured B cells"; Internatl. Immunol., 1998, Vol.10, No. 8, pp. 1121-1129. | |
| | 12 | MARTIN A. et al., "AID and mismatch repair in antibody diversification"; Nat. Rev. Immunol., 2002, Vol. 2, No. 8, pp. 605-14. | |
| | 13 | MARTIN A. et al., "Somatic hypermutation of the AID transgene in B and non-B cells"; Proc. Natl. Acad. Sci. USA, 2002, Vol. 99, No. 19, pp. 12304-08. | |
| | 14 | MARTIN A. et al., "Activation-induced cytidine deaminase turns on somatic hypermutation in hybridomas"; Nature, 2002, Vol. 415, pp. 802-6. | |
| | 15 | MURAMATSU M. et al., "Class Switch Recombination and Hypermutation Require Activation-Induced Cytidine Deaminase (AID), a Potential RNA Editing Enzyme"; Cell. 2000, Vol. 102, pp. 553-63. | |
| | 16 | MUSCHEN M. et al., "Somatic Mutation of the CD95 Gene in Human B Cells as a Side-Effect of the Germinal Center Reaction"; J. Exp. Med., 2000, Vol.192, No. 12, pp. 1833-39. | |
| | 17 | OKAZAKI I. et al., "The AID enzyme induces class switch recombination in fibroblasts"; Nature, 2002, Vol. 416, pp. 340-45. | |
| | 18 | PASQUALUCCI L. et al., "BCL-6 mutations in normal germinal center B cells: Evidence of somatic hypermutation acting outside Ig loci"; Proc. Natl. Acad. Sci. USA, 1998, Vol. 95, No. 20, pp. 11816-21. | |
| | 19 | PASQUALUCCI L. et al., "Hypermutation of multiple proto-oncogenes in B-cell diffuse large-cell lymphomas"; Nature, 2001, Vol. 412, pp. 341-6. | |
| | 20 | PETERS A. et al., "Somatic Hypermutation of Immunoglobulin Genes Is Linked to Transcription Initiation"; Immunity, 1996, Vol. 4, pp. 57-65. | |

| | | | |
|--------------------|--|-----------------|--|
| Examiner Signature | | Date Considered | |
|--------------------|--|-----------------|--|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**

(Use as many sheets as necessary)

Complete if Known

| | |
|--------------------------------|----------------|
| Application Number | 10/501,628 |
| Filing Date (I.A. Filing Date) | 01/15/2003 |
| First Named Inventor | Alberto Martin |
| Art Unit | to be assigned |
| Examiner Name | to be assigned |
| Attorney Docket Number | 96700/905 |

Sheet 3 of 4

NON PATENT LITERATURE DOCUMENTS

| Examiner Initials* | Cite No. ¹ | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T ² |
|--------------------|-----------------------|---|----------------|
| | 21 | PETERSEN-MART S. K. et al., "AID mutates E. coli suggesting a DNA deamination mechanism for antibody diversification"; Nature, 2002, Vol. 418, pp. 99-104. | |
| | 22 | POLTORATSKY V. et al., "Error-prone Candidates Vie for Somatic Mutation"; J. Exp. Med., 2001, Vol. 192, No. 10, pp. F27-F30. | |
| | 23 | RADA C. et al., "The intrinsic hypermutability of antibody heavy and light chain genes decays exponentially"; EMBO J., 2001, Vol. 20, No. 16, pp. 4570-6. | |
| | 24 | REVV P. et al., "Activation-Induced Cytidine Deaminase (AID) Deficiency Causes the Autosomal Recessive Form of the Hyper-IgM Syndrome (HIGM2)"; Cell, 2000, Vol. 102, No. 5, pp. 565-75. | |
| | 25 | SALE J.E., et al., "TdT-Accessible Beaks Are Scattered over the Immunoglobulin V Domain in a Constitutively Hypermutating B Cell Line"; Immunity, 1998, Vol. 9, No. 6, pp. 859-69. | |
| | 26 | SHEN H.M. et al., "Mutation of BCL-6 Gene in Normal B Cells by the Process of Somatic Hypermutation of Ig Genes"; Science, 1998, Vol. 280, pp.1750-52. | |
| | 27 | SHEN H.M. et al., "The TATA binding protein, c-Myc and survivin genes are not somatically hypermutated, while Ig and BCL6 genes are hypermutated in human memory B cells"; Intl. Immunol., 2000, Vol. 12, No. 7, pp. 1085-93. | |
| | 28 | SPENCER J. et al., "Characteristics of Sequences Around Individual Nucleotide Substitutions in IgV-H Genes Suggest Different GC and AT Mutators"; J. Immunol., 1999, Vol.162, No. 11, pp. 6596-601. | |
| | 29 | TUMAS-BRUNDAGE K. et al., "The Transcriptional Promoter Regulates Hypermutation of the Antibody Heavy Chain Locus"; J. Exp. Med., 1997, Vol. 185, No. 2, pp. 239-50. | |
| | 30 | YELAMOS J. et al., "Targeting of non-Ig sequences in place of the V segment by somatic hypermutation"; Nature, 1995, Vol. 376, No. 6537, pp. 225-29. | |

| | |
|--------------------|-----------------|
| Examiner Signature | Date Considered |
|--------------------|-----------------|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

| | | | | | |
|--|---|--------------------------------|----------------|------------------------|-----------|
| Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i> | | Complete if Known | | | |
| | | Application Number | 10/501,628 | | |
| | | Filing Date (I.A. Filing Date) | 01/15/2003 | | |
| | | First Named Inventor | Alberto Martin | | |
| | | Art Unit | to be assigned | | |
| | | Examiner Name | to be assigned | | |
| Sheet | 4 | of | 4 | Attorney Docket Number | 96700/905 |

| NON PATENT LITERATURE DOCUMENTS | | | |
|---------------------------------|-----------------------|---|----------------|
| Examiner Initials* | Cite No. ¹ | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T ² |
| | 31 | YOSHIKAWA K. et al., "AID Enzyme-Induced Hypermutation in an Actively Transcribed Gene in Fibroblasts"; Science, 2002, Vol. 296, No. 5574, pp. 2033-6. | |
| | 32 | ZAN H. et al., "Induction of Ig Somatic Hypermutation and Class Switching in a Human Monoclonal IgM+ IgD+ B Cell Line In Vitro: Definition of the Requirements and Modalities of Hypermutation" J. Immunol., 1999, Vol. 162, No. 6, pp. 3437-47. | |
| | 33 | ZAN H. et al., "B Cell Receptor Engagement and T Cell Contact Induce bcl-6 Somatic Hypermutation in Human B Cells: Identity with Ig Hypermutation"; J. Immunol., 2000, Vol. 165, No. 2, pp. 830-9. | |
| | 34 | ZHANG W. et al., "Clonal instability of V region hypermutation in the Ramos Burkitt's lymphoma cell line"; Intl. Immunol., 2001, Vol. 13, No. 9, pp. 1175-84. | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

| | | | |
|--------------------|--|-----------------|--|
| Examiner Signature | | Date Considered | |
|--------------------|--|-----------------|--|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.